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animaux recevaient alors une perfusion d'urée à 30 p. cent dans une solution de sucre inverti à 10 p. cent (Javid, 1958) au rythme de 3 cm^3/mn pendant une heure. Alors que le pH, la $PaCO^2$ et HCO_3- restaient pratiquement inchangés, la pression intracrânienne redescendait à sa valeur de contrôle, et même plus bas, pour ne remonter ensuite que très lentement.

CONCLUSION

Ces résultats permettent d'individualiser les deux composantes de l'hypertension intracrânienne par compression mécanique directe du cerveau. Ils montrent, en outre, que l'action du T.H.A.M. sur cette hypertension est limitée à son élément acidosique alors que la correction de l'élément purement compressif est réalisée au maximum par l'urée. Probablement, ainsi qu'il a été suggéré récemment (Stubbs et Pennybacker, 1960), le traitement de ce type d'hypertension cérébrale devrait tenir compte de cette dualité.

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SUMMARY

Intracranial hypertension was artificially induced in dogs by blowing up a small rubber balloon inserted beneath the dura. The consequences of elevations of pressure reaching four to six times control values were treated with tri (hydroxymethyl) aminomethane (T.H.A.M.). Elevations in intracranial pressure that interfered with the mechanism of respiration resulted in hypoventilation and respiratory acidosis. T.H.A.M., a buffer and a diuretic, helped reestablish normal pressure and acid-base equilibrium. With normal breathing and in the absence of acidosis, administration of urea intravenously was a satisfactory method of restoring intracranial pressure to its control level by osmotic action.

Comparative Clinical Study of Two Hypnotic Drugs

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THE description which follows is one from a series of comparative studies of drugs with hypnotic characteristics. A controlled clinical study was conducted to compare the sleep-inducing and sleep-sustaining characteristics of two non-barbiturate hypnotics, ethchlorvynol (Placidyl*) and glutethimide (Doriden). Both drugs were given in 0.5-g. dosage. These drugs are in use as night-time sedatives (hypnotics) in every-day medical practice.

ABSTRACT

The comparative sleep-inducing and sleep-sustaining effects of glutethimide, 0.5 g., and ethchlorvynol, 0.5 g., were studied in 20 patients hospitalized for a considerable time (average: 21 years; minimum nine years and maximum 32 years) and not receiving psychotropic agents. Assessment of sleep and para-sleep parameters (pre-sleep tension; frequency of awakening at night; post-sleep activity) revealed that patients fell asleep faster (P>.001) and slept for a longer time with ethchlorvynol than with glutethimide.

METHOD AND PROCEDURE[1]

The trial was carried out as a placebo-controlled, double-blind, six-day experiment, with a cross-over design. All three compounds—ethchlorvynol, glutethimide and placebo—were administered twice during the trial. Criteria for selection of the sample group were the patient's willingness to co-operate in the experiment, and the fact that the patient was not receiving any other psychotropic medication. It should be noted that all patients selected for this study had been hospitalized for a considerable time, the average length of hospitalization being 21 years; the minimum was nine years and the maximum was 32 years.

The subjects were moved into two bedrooms, a large one containing 18 beds and an adjacent room containing two beds. The ordinary routine of the patients was modified in the following manner. Patients were not permitted in the bedrooms or allowed to sleep during the day. Breakfast time was rearranged to allow them to sleep as long as they desired. In the evening, they were asked to go to bed at 8:45 p.m., at which time the emotional tension level of each patient was recorded. A rating scale was devised for this purpose, ranging from "1", indicating no apparent tension, to "4", indicating that the patient was highly agitated. At 9 p.m.

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medication was given, without comment, and thereafter a check was made every 15 minutes to ascertain if the patient was asleep. A patient was judged to be asleep if he did not turn over or move when a flashlight was focused on him. The time which elapsed from the administration of the medication until the patient fell asleep was measured, as was the frequency of getting up during the night. The time of each patient's awakening in the morning was registered, and his activities during the subsequent morning hours were noted. Here again, a "1-4" rating scale was used: "1" indicating that the patient engaged in everyday activity and "4" that the patient remained in bed after awakening.

In order to effect the cross-over design, the patients were subdivided into two groups. The method of administration of the drugs is presented in Table I.

TABLE I.

Day	*Group A*	*Group B*
1	Med. A	Med. B
2	" C	" A
3	" B	" C
4	" A	" B
5	" C	" A
6	" B	" C

Patients were subdivided into two groups to facilitate the operation of the cross-over design. The key to the medication is as follows: Med. A—placebo; Med. B—glutethimide; Med. C—ethchlorvynol.

RESULTS

The results of this study are presented in Table II.

TABLE II.

	Pre-sleep tension	*Onset of sleep (in min.)*	*No. of times up at night*	*Duration of sleep (in min.)*	*Post-sleep activity*
Glutethimide, 0.5 g., 1 tablet	1.2	100.0	0.8	487.3	1.2
Ethchlorvynol, 0.5 g., 1 tablet	1.1	64.5	1.0	500.2	1.9
Placebo (1 tablet)	1.3	86.7	0.5	468.2	1.6

Means of the sleep-inducing and sleep-sustaining characteristics of the administered compounds.

The data were then subjected to statistical analysis (t test). The differences between glutethimide and placebo proved to be statistically non-significant. When ethchlorvynol and glutethimide were compared in regard to the onset of sleep, the results at the $P>.001$ level proved significant. This was also the case in the comparison of ethchlorvynol and placebo, which showed significant results at the $.05>P>.02$ level. None of the other findings reached statistical significance.

DISCUSSION

The main results, as revealed in the tables, suggest that of the drugs tested, ethchlorvynol, in the dosage chosen, was the more effective hypnotic. Subjects on this drug fell asleep faster and remained asleep for a longer time than those on glutethimide, although results with the latter did not reach statistical significance. It becomes apparent from Table II that there were no meaningful differences in the level of pre-sleep tension, frequency of wakening at night or post-sleep activity, in patients from either group. Placebo administration resulted in a distinctly inferior effect when compared to ethchlorvynol. No side effects were observed with either of the active medications or placebo. Owing to their lengthy hospitalization it could be predicted that these patients, in the event of subjective discomfort, would frequently fail to communicate this or to complain to their attendant staff. Thus, in order to avoid possible concealment of side effects, a special three-day study was conducted, similar to the original design, but this time patients were specifically questioned regarding side effects. The results of this study were negative, again no side effects being found.

We realize that our sample of chronic, hospitalized, psychiatric patients differs from the general population of ambulant patients requiring hypnotics, but nevertheless we consider that it is a valid one for the comparison of the properties of the medications tested.

SUMMARY

The effects of two non-barbiturate hypnotic compounds were compared to each other and to a placebo, in a clinical, controlled experiment. As judged by the sleep and para-sleep parameters assessed, ethchlorvynol (0.5 g.) appeared to have more pronounced hypnotic characteristics than glutethimide (0.5 g.).

We are indebted to Miss M. Henry for her help in the preparation of this study.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

Rational scientific therapeutics today demands that treatment be directed, not to mere symptoms, but to the underlying cause, whether this be of the nature of an infection by a specific micro-organism, or of an overactivity or deficiency in some internal secretion, or whether it arise from an interference with normal physiological processes in the body due to an infraction of the laws of health. It demands from the physician a knowledge of normal structure and function, and of the changes which may be wrought in both by disease, so that he may be able to trace clinical symptoms back to the histologic alterations which produce them, and thus distinguish between the pathological process and its mere symptomatic manifestations.—A. D. Blackader: "The Therapeutics of Today", The Address in Medicine presented at the Forty-fifth Annual Meeting of the C.M.A., *Canad. Med. Ass. J.*, 2: 864, 1912.